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<p>(21) International Application Number: PCT/DK98/00543 (22) International Filing Date: 9 December 1998 (09.12.98) (30) Priority Data: 1441/97 11 December 1997 (11.12.97) DK (71) Applicant (for all designated States except US): M D FOODS A.M.B.A. [DK/DK]; Skanderborgvej 277, DK-8260 Viby J (DK). (72) Inventors; and (75) Inventors/Applicants (for US only): HOLST, Hans, Henrik [DK/DK]; Rosenallé 86, DK-6920 Videbæk (DK). CHAT- TERTON, Derek, E., W. [GB/DK]; Præstevangsvej 37, DK-8210 Århus V (DK). (74) Agent: HOFMAN-BANG & BOUTARD, LEHMANN & REE A/S; Hans Bekkevolds Allé 7, DK-2900 Hellerup (DK).</p>		<p>(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report.</p>
<p>(54) Title: A PROCESS FOR PREPARING A KAPPA-CASEINO GLYCOMACROPEPTIDE OR A DERIVATIVE THEREOF</p> <p>(57) Abstract</p> <p>Improved process for preparing a kappa-caseino glycomacropeptide and derivatives thereof which comprises adjusting the pH of a solution of a milk starting material to below 4, cold ultrafiltration and concentration of the starting material on a spiral filter. This process is usable in industrial scale without fouling problems and without damaging the usable milk material by-product.</p>		

A process for producing a kappa-caseino glycomacropeptide or a derivative thereof.

The present invention relates to an improvement of a
5 process for producing kappa-casein glycomacropeptide,
GMP, κ -caseinoglycopeptide, CGP or caseinomacropeptide,
CMP or a derivative thereof without destroying the milk
starting material, in particular whey, which is a useful
by-product. This improved process is useful in a indu-
10 strial scale at commercial way - not just useful in the
laboratory.

GMP has numerous useful possible applications.

15 US 4 994 441 proposed to use GMP in a composition for
treating and inhibiting formation of dental plaque and
caries, for example in a tooth paste.

US 5 063 203 proposed to use κ -caseinoglycopeptide for
20 the manufacture of a composition, in particular a medica-
ment, for the prevention and/or the treatment of thrombi.

Further GMP or CGP has been proposed to stimulate bifido-
bacterial growth making it useful in dietetic food pro-
25 ducts i.a. for infants, and prevention of binding of
cholera toxin to its receptor.

GMP has also been suggested for use in the treatment of
disorders in amino acid metabolism, such as phenylke-
30 touria (PKU).

Many attempts have been undertaken to find useful pro-
cesses to prepare GMP. Most of them are not industrially
usable.

WO 94/15952 relates to a method for production of a kappa-casein glycomacropeptide i.a. comprising heat treatment of a whey product. This causes a denaturation of the whey by-product so that it will be unsuitable for other purposes.

EP 0 453 782 has proposed a process for the production of kappa-caseinoglycomacropeptide in which the proteins of a whey product concentrated with proteins partly freed from lactose are flocculated, resulting in a precipitate and a first supernatant, and the first supernatant is concentrated by ultrafiltration, leading to a retentate, which is then treated with ethanol, which produces a precipitate and a second supernatant, the second supernatant is collected and then dried. This process is very inconvenient and troublesome.

EP 0 393 850 and US 5 075 424 relate to a process for producing a kappa-casein glycomacropeptide which comprises adjusting the pH of a solution of milk starting materials containing the kappa-casein glycomacropeptide to below 4, treating the solution by ultrafiltration with a membrane passing a molecular weight fraction of 10,000 to 50,000, and concentrating the filtrate obtained with a membrane passing a molecular weight fraction of 50,000 or less.

The concentration can be performed on the same filter by readjustment of pH to 4 or higher, typically 6.5, or on another membrane having a smaller cut-off value under 10,000.

This known process has a high production cost, gives an impure product, and the filter is fast fouled during the filtration by protein and must often be cleaned. The process gives a poor yield. A diluted starting solution

is used in order to reduce fouling. The diluted starting solution requires use of large amounts of water and more energy. A typical starting solution is a solution having a protein content of 2 % by weight.

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EP 0 488 589 relates to a process for producing a kappa-casein glycomacropeptide comprising contacting milk raw materials containing the kappa-casein glycomacropeptide with an ion exchanger, collecting a fraction which does
10 not adsorb on the ion exchanger, and concentrating and desalting the fraction to obtain the kappa-casein glycomacropeptide. This process is rather convenient because it is easy to perform and it does not damage the whey by-product. However deposits on the ion exchanger are a
15 problem, so it has to be cleaned and replaced rather often. The applicant of EP 0 393 850 tries to overcome the problem of protein fouling during filtration by removing proteins by this process using an ion exchanger.

20 It has now surprisingly been shown that an improvement of the process known from EP 0 393 850 as stated in the following, prevents the drawbacks of the known processes.

The process according to the invention is of the known
25 type which comprises adjusting the pH of a solution of milk starting materials containing the kappa-casein glycomacropeptide or derivatives thereof to below 4, treating the solution by ultrafiltration with a membrane passing a molecular weight fraction of 10,000 to 50,000, and
30 after adjustment of pH to above 4 concentrating the filtrate obtained with a membrane passing a molecular weight fraction of 50,000 or less. The process of the invention is characterized in that cold ultrafiltration is applied using a spiral filter.

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The process of the invention gives a pure product in a high yield and at a low cost without denaturing the valuable whey by-product. The process gives a better bacteriological control.

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Ultrafiltration is preferably carried out at a temperature below 15 °C, especially 7 to 15 °C. For the time being it is preferred to use about 12 °C.

- 10 The starting material can be a whey product. It is preferred to use a concentrated whey product, such as a whey product having a content of above 15, especially 35 to 80 and most preferred 85 to 95 % by weight protein based on the dry matter content. Preferred whey products are whey
15 protein concentrate, WPC and whey protein isolate, WPI. Consequently is it possible to reduce the amount of energy and water needed in the process.

- The process of the invention can be carried out using a
20 concentration of 0.8 to 15 % by weight of protein , 5 to 15, especially 6 to 8 % by weight is preferred. For the time being 7 % by weight is the most preferred concentration.

- 25 A FV membrane from OSMONICS-DESALINATION, Vista, California, USA is a usable membrane. Other firms have corresponding membranes usable in the invention.

- The ultrafiltration can be improved by using a filter
30 aid. It is surprising that calcium phosphate can be used, because one should expect that it had a tendency to dissolve in the acid solution. It is preferred to use milk based calcium phosphate, especially if the GMP prepared by the invention has to be used in food or the like.

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The ultrafiltration can be carried out at a pH of 2.5 to 3.5, 2.8 to 3.2 being a preferred range, and for the time being a pH of 3.0 is preferred.

The invention is further illustrated by the following
5 examples.

EXAMPLE 1:

250 litres of WPC concentrate containing 30% dry matter and 23% protein was diluted with 750 litres of demineral-
10 ized cold water, which left 7.50% dry matter and 5.75% protein in the dilution. 12 N hydrochloric acid was added until the pH was 3.1.

Ultrafiltration I: The solution was filtered on two UF
15 spiral elements of the type FV6338C from OSMONICS-DESALINATION having a cut-off value of 20,000 Daltons. Before the filtration the membranes were coated with 500 g of suspended calcium phosphate product. The total membrane area was 31 m². The filtration was carried out under the following conditions: The temperature was maintained at approximately 15 °C, the mean pressure was maintained at 3 bars with a feeding pressure of 2 bars. The pH was maintained at 3.1 by using 12 N HCl, and cold demineralized water was added with the same flow as permeate was removed. The recirculation flow in the loop was
20 16 m³/h, and the recirculation over the feeding tank was approximately 5 m³/h. After a 7 hour filtration the addition of demineralized water to the feeding tank was stopped. Subsequently a concentration was carried out until the dry matter in the feeding tank was 15%. The mean
25 flux was measured to 36.1 l/m²h. 28% sodium hydroxide was added to the permeate until the pH was 6.7.

Ultrafiltration II: The pH adjusted permeate from ultrafiltration I was then ultrafiltered at pH 6.7 on two
35 ultrafiltration spiral elements of the type HFK328

6338NYT from KOCK, Wilmington, MA, USA having a cut-off value of 5,000 Daltons. The filtration was carried out under the following conditions: The temperature was maintained at 15 °C, the mean pressure was maintained at 4 bars. Same flow as under ultrafiltration I. After concentration a diafiltration was carried out to demineralize the solution. After filtration the concentrate was dried in a pilot spray dryer. 5.0 kg of powder having the composition indicated in the subsequent table was obtained.

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EXAMPLE 2:

200 litres of WPC concentrate containing 30% dry matter and 23% protein was diluted with 400 litres of demineralized cold water, which left 10.00% dry matter and 7.67% protein in the dilution. 12 N hydrochloric acid was added until the pH was 2.8.

Ultrafiltration I: The solution was filtrated on two ultrafiltration spiral elements of the type FV6338C from OSMONICS-DESALINATION having a cut-off value of 20,000 Daltons. Before the filtration the membranes were coated with 500 g of suspended calcium phosphate product. The total membrane area was 31 m². The filtration was carried out under the following conditions: The temperature was maintained at approximately 12 °C, the mean pressure was maintained at 3.5 bars with a feeding pressure of 2.5 bars. The pH was maintained at 3.0 by using 12 N HCl, and demineralized cold water was added with the same flow as permeate was removed. The recirculation flow in the loop was 16 m³/h, and the recirculation over the feeding tank was approximately 5 m³/h. After an eight-hour filtration the filtration was stopped. The mean flux was 21.1 l/m² h. 28% sodium hydroxide was added to the permeate until the pH was 6.7.

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Ultrafiltration II: The pH adjusted permeate from ultrafiltration I was ultrafiltered at pH 6.7 on two ultrafiltration spiral elements of the type HFK328 6338NYT from KOCK having a cut-off value of 5,000 Daltons. The filtration was carried out under the following conditions: The temperature was maintained at 12 °C, the mean pressure was maintained at 4 bars. Same flow as under ultrafiltration I. After concentration a diafiltration was carried out to demineralize the solution. After filtration the concentrate was dried in a pilot spray dryer. 4.2 kg of powder containing 79.5% protein was obtained, the 90% being GMP.

COMPARATIVE EXAMPLES:

In the two subsequent tests, which are comparative tests, it has been attempted to repeat example 1 of the EP 0 393 850 patent as far as possible: 100 litres of WPC concentrate containing 30% dry matter and 23% protein was diluted with 1300 litres of demineralized water heated to 55 °C, which left 2.14% dry matter and 1.64% protein in the dilution. 12 N hydrochloric acid was added until the pH was 3.5.

Ultrafiltration I: The solution was filtered on a module 38 from DDS fitted with GR61PP membranes from DOW with a cut-off value of 20,000 Daltons. The module has an area of 42 m² divided in five sections. The filtration was carried out under the following conditions: The temperature was maintained at 50 °C, the mean pressure was maintained at 4 bars, the pH was maintained at 3.5 by using 12 N hydrochloric acid, and 50 °C hot demineralized water was added to the feeding tank at a speed of 90% of the permeate flow so that the concentration of dry matter and protein in the feeding tank was increasing very slowly. The recirculation in the loop was 42 m³/h, and the recirculation over the feeding tank was approximately 5 m³/h.

When 8000 litres of permeate has been removed, the filtration was stopped. The mean flux was measured to 46.7 l/m²h. 28% sodium hydroxide was added to the permeate until the pH was 7.0.

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Ultrafiltration II: The pH adjusted UFI permeate from ultrafiltration I was then ultrafiltered in the same plant again at 50 °C, the mean pressure being maintained at 4 bars, and the pH being maintained at 7.0 by using sodium hydroxide. Same flow as under ultrafiltration I. The concentrate was diafiltered in order to demineralize the solution. After filtration the concentrate was dried in a pilot spray dryer.

15 EXAMPLE 3:

A GMP powder was prepared by means of the same procedure as described in example 1 of EP 0 393 850.

A DDS module 38 UF plant fitted with GR61PP membranes was used for the test. The membranes had been in use for approximately 200 hours exclusively with whey protein products. In the patent EP 0 393 850 it is stated that when this procedure is followed, a GMP product having a purity of 82% was obtained.

25

3.3 kg powder having the composition described in the table below was obtained.

EXAMPLE 4:

30 Example 3 was repeated at a temperature of 10 - 15 °C instead of at the preferred temperature of 50 °C. The test was carried out in the same plant fitted with the same membranes.

35 The GMP powders have the following composition and are here compared with a standard WPC product LACPRODAN-80

and a GMP product obtained by means of the process according to the invention.

5

T A B L E

	Product according to example 3	Product according to example 4	Standard product	Product according to example 1 (of the invention)
Dry matter	92.8	92.7	94.7	94.3
Protein	81.0	81.2	77.7	79.2
Protein/dry matter	87.3	86.5	82.0	84.0
Fat	6.22	6.62	6.30	0.13
Lactose	0.03	0.29	5.20	0.05
pH	6.23	6.56	6.46	6.45
Mineral	2.71	2.90	2.63	6.89
Phosphorus	0.339	0.330	0.310	0.576
Chloride	<0.05	<0.05	<0.05	<0.05
Calcium	0.533	0.423	0.380	0.979
Potassium	0.106	0.125	0.600	2.310
Magnesium	0.076	0.057	0.064	0.133
Sodium	0.423	0.598	0.190	0.091
α -la	12.3	11.4	9.8	3.4
β -lg	47.8	46.8	39.0	<0.5
NPN% of protein	24.6	30.7	23.9	>96
Sialic acid/protein	1.79	1.37	1.56	5.55

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As is seen, the difference between the product according to example 3 and the standard product is that there is more protein and less lactose in the product prepared according to EP 0 393 850 than in the standard product. The contents of the other components are on the whole the

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same in the two products both as regards sialic acid and NPN (=GMP+PP). The NPN analysis gives the amount of GMP in the products due to lack of proteose peptone, PP. The reason why the GMP product obtained according to
5 EP 0 393 850 is not as pure as the patent claims, is that we have employed "used" membranes. If we had inserted new membranes before the test, we had no doubt obtained a "purer" product, since it is known to the inventor of the present application that DCW's plate and frame membranes,
10 such as GR61PP, rapidly change their filtration properties, especially in the case of hot filtration (50 °C). During the first filtration the permeate should consist of "pure" GMP. However, from the FPLC chromatograms both α -lactalbumin, α -la and β -lactoglobulin, β -lg are seen in
15 the permeate. During the second filtration some of the GMP is on the other hand lost to the permeate as the membranes are not tight enough owing to pin point holes. From this test it can be concluded that if attempts are made to produce GMP according to the procedure mentioned
20 in EP 0 393 850 on GR61PP membranes which are not new, a product which does not differ essentially from a standard product is obtained.

As appears from the analytical results, the product according to example 1 is very different from the two other
25 products (example 3 and 4) as far as the protein composition is concerned (high concentration of NPN and very low concentration of α -la and β -lg). The mineral content is also very different, more than double the amount of mineral content. It is known that GMP binds large quantities
30 of minerals.

DIFFERENCES BETWEEN THE PROCESS ACCORDING
TO EP 0 393 850 (example 3) AND THE PROCESS ACCORDING TO
35 THE INVENTION (examples 1 and 2).

The process of the invention as illustrated in the examples 1 and 2 differs from the known process on the following points:

- 5 The temperature: The process of the invention use cold filtration (typically temperatures below 15 °C), whereas all the examples in EP 0 393 850 uses hot filtration (50 °C). When using cold filtration, the membranes last longer, and the retention is also a good deal different
- 10 (more tight membranes). Moreover, the bacteriological quality is better when cold filtration is used. To prove that cold filtration is better, we have made the test described in example 4. From the results it appears that the NPN (= GMP - PP) content has increased from 24.6% to
- 15 30.7% of the protein content. This indeed proves that a purer product is obtained by cold filtration than by hot filtration. The greatest difference is that only a little GMP is lost during the concentration.
- 20 The membrane: In all the examples in EP 0 393 850 use was made of DOW GR61PP membranes on the plate and frame system. This system was the prevailing system in the period where they invented the process. The GR61PP membranes have a bad mechanical durability. The examples of inven-
- 25 tion make use of a very special membrane: FV from OSMONICS-DESALINATION which has shown a very good mechanical stability. The same permeability was observed after one year of use, as when it was installed in a plant which was in production 24 hours seven days a week.
- 30 The feed: The known process starts with a very weak solution (2% dry matter) and ultra-/diafiltration of this solution, probably because the GMP product becomes more impure if a greater dry matter content is used in the feed.
- 35 The process of the invention (examples 1 and 2) starts with a dry matter content of approximately 7%. This means

that a considerably smaller quantity of water has to be used in order to wash out the same quantity of GMP. The known process uses 12.300 litres/kg GMP. The process of the invention uses 1.880 litres/kg GMP.

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Membrane coating: It has turned out that when the membrane is coated with filter aid, especially with calcium phosphate, before starting the production, the GMP permeability becomes approximately double as large as when the
10 membrane is not coated. To substantiate that coating gives a positive effect, the following two tests were carried out:

EXAMPLE 5:

15 200 litres of WPC retentate with 30% dry matter and 23% protein was diluted with 800 litres of demineralized water, and the pH was adjusted to 3.0 by using 30% hydrochloric acid.

20 This solution was filtered on two ultrafiltration spiral elements of the type FV with and without coating with 500 g calcium phosphate under the following conditions:

Temperature: 10 - 12 °C. Booster flow: 16 m³/h. Feeding
25 pressure: 2 bars. Retentate flow to the feeding tank: 5 m³/h. After reaching 7% dry matter diafiltration was carried out with the same flow as the permeate flow. The pH was maintained at 3.0 during the whole filtration. Permeate samples were collected after 5 min. and then after
30 each hour. The samples were analysed on HPLC for GMP and α -lactalbumin.

The following results were obtained:

	With $\text{Ca}_3(\text{PO}_4)_2$		Without $\text{Ca}_3(\text{PO}_4)_2$	
	α -la %	GMP %	α -la %	GMP %
5 min.	0.010	0.207	0.010	0.088
1 hour	0.009	0.193	0.008	0.144
2 hours	0.007	0.131	0.007	0.121
3 hours	0.009	0.121	0.008	0.117
4 hours	0.010	0.101	0.008	0.105
5 hours	0.009	0.080	0.013	0.122

The reason why the GMP content in the permeate with coating fell much towards the end is that there was not much GMP left in the retentate. In the test without coating there was still some GMP left after 5 hours' running. The conclusion is that coating has the effect that GMP can be washed out much quicker than without coating.

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ANALYSIS METHODS

The NPN analysis employed differs somewhat from other NPN analysis. The following procedure is used:

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- 1: Dissolve 15 g of powder in 285 g of demineralized water.
- 2: pH adjust the solution to 6.5 by using 10% HCl or 10% NaOH.
- 20 3: The solution is analysed for total protein (Kjeldahl).
- 4: The rest is heat treated in closed glass at 90 °C for 60 min.
- 5: Cooling to room temperature.
- 25 6: pH adjustment to 4.6 by using 30% HCl.
- 7: Centrifugation at 15,000 g for 10 min.

8: Filter supernatant by means of a non-nitrogen containing filter.

9: The filtrate is analysed for total protein.

PR_1 = Protein content in the solution before heat

5 treatment.

PR_2 = Protein content in the filtrate after heat

treatment.

$$\text{NPN protein} = (PR_2 \cdot 100) / PR_1.$$

CLAIMS:

1. A process for producing kappa-caseino glycomacropeptide or a derivative thereof, which comprises adjusting
5 the pH of a solution of milk starting materials containing the kappa-caseino glycomacropeptide or a derivative thereof to below 4, treating the solution by ultrafiltration with a membrane passing a molecular weight fraction of 10,000 to 50,000, and after adjustment of pH to above
10 4 concentrating the filtrate obtained with a membrane passing a molecular weight fraction of 50,000 or less,

c h a r a c t e r i z e d in that the ultrafiltration is carried out in the cold using a spiral filter.
15
2. A process according to claim 1, c h a r a c t e r i z e d in that the ultrafiltration is carried out at a temperature below 15 °C.
- 20 3. A process according to claim 1 or 2, c h a r a c t e r i z e d in that the ultrafiltration is carried out at a temperature of 7 to 15 °C.
4. A process according to any of the preceding claims,
25 c h a r a c t e r i z e d in that the temperature is 12 °C.
5. A process according to any of the preceding claims, c h a r a c t e r i z e d in that the starting material
30 is a whey product.
6. A process according to claim 5, c h a r a c t e r i z e d in that the starting material is a whey product having a content of above 15 % by weight protein based on
35 dry matter.

7. A process according to claim 6, c h a r a c t e r i -
z e d in that the starting material is a whey product
having a content of 35 to 80 % by weight protein based on
dry matter.

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8. A process according to claim 7, c h a r a c t e r i -
z e d in that the starting material is a whey product
having a content of 85 to 95 % by weight protein based on
dry matter.

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9. A process according to claim 5, c h a r a c t e r i -
z e d in that the starting material is a whey protein
concentrate, WPC.

15

10. A process according to claim 5, c h a r a c t e r i -
z e d in that the starting material is a whey protein
isolate, WPI.

20

11. A process according to any of the preceding claims,
c h a r a c t e r i z e d in that the starting material
is used in a concentration of 0.8 to 15 % by weight of
protein in the solution.

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12. A process according to any of the preceding claims,
c h a r a c t e r i z e d in that the starting material
is used in a concentration of 5 to 15 % by weight of pro-
tein in the solution.

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13. A process according to any of the preceding claims,
c h a r a c t e r i z e d in that the starting material
is used in a concentration of 6 to 8 % by weight of pro-
tein in the solution.

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14. A process according to any of the preceding claims,
c h a r a c t e r i z e d in that the starting material

is used in a concentration of 7 % by weight of protein in the solution.

15. A process according to any of the preceding claims,
5 characterized in that the membrane is a "FV membrane" from OSMONICS-DESALINATION or a corresponding membrane.
16. A process according to any of the preceding claims,
10 characterized in that the ultrafiltration is carried out on a membrane coated with a filter aid.
17. A process according to claim 16, characterized in that the filter aid is calcium phosphate.
15
18. A process according to claim 17, characterized in that the filter aid is milk based calcium phosphate.
19. A process according to any of the preceding claims,
20 characterized in that the ultrafiltration is carried out at a pH of 2.5 to 3.5.
20. A process according to any of the preceding claims,
25 characterized in that the ultrafiltration is carried out at a pH of 2.8 to 3.2.
21. A process according to any of the preceding claims,
30 characterized in that the ultrafiltration is carried out at a pH of 3.0.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 98/00543

A. CLASSIFICATION OF SUBJECT MATTER		
IPC6: A23J 1/20, C07K 14/47, C07K 1/34 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols)		
IPC6: C07K, A23J		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
SE,DK,FI,NO classes as above		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0393850 A2 (SNOW BRAND MILK PRODUCTS CO., LTD.), 24 October 1990 (24.10.90)	1-21
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A	US 4125527 A (MARCEL BUHLER ET AL), 14 November 1978 (14.11.78), column 3, line 11 - line 15	1-21
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<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "F" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
22 March 1999		24 -03- 1999
Name and mailing address of the ISA: Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86		Authorized officer Patrick Andersson Telephone No. +46 8 782 25 00

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Information on patent family members

02/03/99

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